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Focal infection: new age or ancient history?

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A focus of infection is a confined area that: (1) contains pathogenic microorganisms, (2) can occur anywhere in the body and (3) usually causes no clinical manifestations (1). A focal infection is a localized or generalized infection caused by the dissemination of microorganisms or toxic products from a focus of infection (1). These concepts have led to the Focal Theory of Infection (or Theory of Focal Infection) that postulates a myriad of diseases caused by microorganisms (bacteria, fungi, viruses) that arise endogenously from a focus of infection. Some have expanded this to include the environment via the concept of antigenic (molecular) mimicry or even to the extent that all diseases are caused by microbes (2, 3).

Foci of infection have historically been postulated to arise from the tonsils, adenoids, sinuses and oral cavity with less common foci from the prostate, appendix, gall bladder and kidney (4, 5). Oral foci have traditionally been ascribed to pyorrhea alveolaris (periodontitis), alveolar abscesses and cellulitis, pulpless teeth, apical periodontitis, general oral sepsis and endodontically treated teeth with viridans group streptococci (VGS) being the principal metastatic microbial culprits (1, 4, 5).

Focal infections attributed to foci of infection have included arthritis, neuritis, myalgias, nephritis, osteomyelitis, endocarditis, brain abscesses, prosthetic joint infections, skin abscesses, pneumonia, asthma, anemia, indigestion, gastritis, pancreatitis, colitis, diabetes, emphysema, goiter, thyroiditis, Hodgkin's disease, fever of unknown origin, stupidity and 'nervous diseases of all kinds' (1, 6–8). Currently, diseases postulated to be caused by microorganisms include cancer (9), sarcoidosis, multiple sclerosis, amyotrophic lateral sclerosis, autism, Guillain–Barré syndrome, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), Tourette's syndrome, myasthenia gravis, polycystic kidney disease, obesity, Alzheimer's disease, diabetes mellitus and, of particular interest to dentistry, cardiovascular disease (4, 10). Many of these are proposed to affect the host by antigenic mimicry: microbial antigens similar to host antigens that induce an immune response that damages host tissue (11). The classic pathway of focal infection is by direct spread via blood or lymphatic metastasis of the infecting microorganism, its toxic products or tissue-damaging immunologic reactions to the microorganism.

Several characteristics consistently appear throughout the long history of focal infection: (1) theories of disease espoused by authoritative (some might say autocratic) individuals with little or no science to support their theses (doctrine without data), (2) consistent application of focal infection to diseases for which medicine has no good concepts of etiology and/or treatment, (3) consistent and pervasive extrapolation beyond the data and (4) a common disregard for the accepted methodology of science (i.e. controlled studies). Often, the 'disregard syndrome' is apparent: the unintentional failure to cite previous scientific works, scorn for previous sound published data that is not considered 'cutting edge', apparently intentional disregard for already published data that does not conform or even contradicts the position espoused by the investigator or an unintentional lack of regard for relevant literature due to ignorance of the field being investigated (12). 'Reverse Investigation' is not uncommon: start with the conclusion and then gather only the facts that support it. The tendency to programmed conferences is common: only those who are of the same mind are invited and commonly leads to what Jane's Defense Weekly terms 'incestuous amplification': a condition in warfare where one only listens

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to those who are already in lock-step agreement, reinforcing set beliefs and creating a situation ripe for miscalculation. Better to follow the observation of Harry Lime in Graham Greene's 'The Third Man' regarding the value of controversy: '30 years of noisy, violent churning under the Borgias in Italy produced Michaelangelo, Leonardo da Vinci and the Renaissance, while 500 years of peace in Switzerland produced the cuckoo clock.'

This review will attempt to avoid the above pitfalls and rely on evidence rather than authority. The reader is encouraged to consult other discussions of focal infection (4, 5, 13–16). Purported associations between oral microorganisms and systemic disease are meaningless without incidence (how often does the disease occur in a population in a given period of time) and prevalence data (how many in a given population have the disorder). Without this information, the purported association is merely hypothesis generating rather than hypothesis proving. It is also imperative to distinguish between metastatic infections that merely reflect the typical pathology produced by the microorganism but in a different place (a streptococcal-induced liver abscess) and non-typical pathology as seen with PANDAS, cancer and various autoimmune disorders resulting from antigenic mimicry.

One of the facets of microbial metastasis often unappreciated is that microorganisms expend much of their time and energy locating, developing and defending biological niches in which they can prosper. Microbes require very specific growth nutrients, favorable local environments (i.e. pH) and safety from their enemies: other bacteria and viruses and natural host defenses such as defensins, cellular and humoral immunity and cationic microbial peptides. Such is the reason for biofilms. To survive and thrive, microbes have long ago learned to avoid hostile regions of the body. For bacteria to metastasize is for bacteria to often commit suicide.

Even the most ubiquitous of human pathogens (streptococci and staphylococci) may only be such because they possess elaborate adhesive properties that allow them to attach to virtually any body surface (skin and mucosa). *Streptococcus pneumoniae* is abundant in the pharynx, sinuses and lower respiratory tract but has never been isolated from an oral cavity only inches away. For some reason the oral environment is very inhospitable to the pneumococcus. The periodontal pathogens, *Prevotella* and *Porphyromonas*, are only located in the oral cavity and the genitourinary tract, a common finding with oral microorganisms. *Actinobacillus actinomycetemcomitans* has only one biological niche: the oral cavity. A thorough understanding of the long and tortuous history of focal infection and its biology will prevent past mistakes from being repeated today.

Ancient history

The first 'report' of focal infection has been ascribed to Hippocrates who attributed the cure of a case of arthritis to a tooth extraction (17). In the early 1800s, Benjamin Rush, an American physician and signer of the Declaration of Independence, also related arthritis cure to tooth extraction (17). With the advent of the germ theory of disease in England in the 1850s and the United States in the early 1880s (spurred by Koch's demonstration of *Mycobacterium tuberculosis* as the cause of tuberculosis), the newly emerging field of microbiology became, as is common with new discoveries, associated with wildly excessive claims for causation and cure (18). The Autointoxication Theory became immensely popular with the claim that bacterial stasis in the colon caused systemic disease and colonic purging became a treatment for gastric cancer, peptic ulcer, neuritis, headache, endocarditis, stupidity, mental apathy and arthritis among other disorders (8). Still practiced today, its major effect may be to reduce colonization resistance in the colon against foreign pathogens by eliminating the local protective flora.

In 1890, the dentist and physician, WD Miller, published his treatise: *The Micro-Organisms of the Human Mouth: The Local and General Diseases Which are Caused By Them* (19) and a year later in *Dental Cosmos* first used the term: 'focal infection' (20). Miller did not mandate removal of teeth as a focus of infection and also suggested 'treating and filling root canals'. In 1900, the English physician, William Hunter, reported in the *British Medical Journal* on 'Sepsis as a Cause of Disease' listing poor oral health and the expanding use of 'conservative dentistry' (the preservation of the dentition by dental treatment) as a cause of the multitude of diseases attributed to focal infection (21). Hunter's remarks to the medical students at McGill University in Montreal in 1911 ignited the fires of focal infection: 'No man has more reason than I to admire the sheer ingenuity and mechanical skill constantly displayed by the dental surgeon. And no

one has had more reason to appreciate the ghastly tragedies of oral sepsis which his misplaced ingenuity so often carries in its train. Gold fillings, crowns and bridges, fixed dentures, built on and about diseased tooth roots form a veritable mausoleum over a mass of sepsis to which there is no parallel in the whole realm of medicine and surgery. A perfect gold trap of sepsis of which the patient is the proud owner and no persuasion will induce him to part with it, for it cost him much money and covers his black and decayed teeth. The worst cases of anemia, gastritis, obscure fever, nervous disturbances of all kinds from mental depression to actual lesions of the cord, chronic rheumatic infections, kidney diseases, all those which owe their origin to , or are gravely complicated by the oral sepsis produced by these gold traps of sepsis. Time and again I have traced the very first onset of the whole trouble to the period within a month or two of their insertion.' (22, 23)

A careful reading of Hunter's lecture at McGill as reported in the Dental Register reveals that Hunter listed only a single case of dental sepsis: a patient told by his dentist never to remove his partial denture from his mouth under any circumstances (23). In the words of EC Kirk: 'Unfortunately, however, Dr Hunter in his enthusiasm for his cause has failed to make as plain as he should make it the distinction which he has clearly implied between such work skillfully executed and intelligently applied and the monstrous anatomical and physiological insults which are palmed off upon an ignorant public by equally ignorant charlatans under the general term of American crown and bridge work.' (24)

Hunter's observations were made without any attempt at the scientific method and are a classic example of extrapolation beyond the data, but along with Sir William Osler's comments about the 'disgrace' of poor dental health, were very helpful in prompting both the American and British dental associations to attain greater professionalism and eliminate the untrained, undereducated and unscrupulous 'practitioners' by licensing requirements (24). Miller was responsible for promoting greater emphasis on disinfection of instruments so as not to spread infection (25).

The era of focal infection in medicine truly began in 1912 when the physician, Frank Billings (26, 27), formally and independently introduced the concept of focal infection to American physicians via case reports ascribing distant infections to various pathogens but going a further step to claim cures of these afflictions by tonsillectomies and dental extractions that removed various foci of infections. Billings was the first to describe microorganisms cultured from septic arthritis patients that when injected into rabbits also caused arthritis (28).

EC Rosenow (29, 30) was a pupil of Billings and developed the theories of 'elective localization' and 'transmutation', whereby microorganisms could possess affinities for certain body organs and then could alter their biological characteristics (VGS could 'transmute' into pneumococci or beta-hemolytic streptococci). This theory was useful in explaining why other researchers could not duplicate Rosenow's results: the original bacterium injected by Rosenow had 'transmuted' to the different bacteria found by other individuals (31). As many prominent physicians (Charles Mayo and Russell Cecil among others) joined Hunter, Billings and Rosenow in advocating the focal infection theory of disease and its remedy by surgery (4, 5), millions of tonsils, adenoids and teeth were removed in an 'orgy of extractions' as described by Grossman.

Endodontics came under particular scrutiny as many physicians and dentists recommended extraction of all endodontically treated teeth (the '100 percenters') with others recommending removal of all non-vital or 'suspicious' teeth and yet others suggesting that all teeth be removed (diseased or not) for the sake of prevention as well as treatment ('therapeutic edentulation' or 'the clean-sweep') (32). In 1918 the dentist, Josef Novitzky (33), assailed dentists who performed endodontic therapy as 'almost criminal', with others suggesting that dentists who performed crown and bridge work be sentenced to '6 months hard labor' (34).

In the 1920s, Dr Weston Price (35, 36) published a series of rabbit experiments and case reports of remarkable improvements in various medical conditions after dental extractions and asserted that 'practically all' infected non-vital teeth should be removed rather that endodontically treated to prevent or cure focal infections. In a later detailed review of the literature on focal infection and particularly the studies of Rosenow, Grossman noted that Rosenow: 'used massive doses of bacterial inocula of up to 10 mL in volume which were then injected intravenously with the organisms being particularly virulent'. Grossman (37) further remarked that Rosenow's technique: 'so devastates the laboratory animal that lesions are sometimes produced in almost every tissue and organ of the body'.

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The laboratory animal (rat and rabbit) models of infective endocarditis that provide most of the evidence for the causation of endocarditis require that a plastic catheter be placed across the aortic valve and left in place, while a very concentrated bolus of microorganisms is injected intravenously (38). This bolus is commonly 10^6–10^9 colony-forming units (cfus) per milliliter (one million to one billion microorganisms) and results in the death of many of the animals due to overwhelming sepsis and alternately with the survival of some without acquiring endocarditis (38). The magnitude of bacteremia caused by dental treatment procedures and oral hygiene and mastication is 1–12 cfus/mL. The relevance of this animal model to human endocarditis has been questioned regarding the need to leave the catheter in place (otherwise endocarditis does not occur often), the huge bolus of microorganisms compared to the human model, the animal disease produced, which is much more acute than the human and the sometimes very high doses of antibiotics necessary to prevent endocarditis in this animal model (38). It is also apparent that not all streptococcal species possess the same virulence factors needed to produce endocarditis and that many vary in their adhesive properties (38). Things can be made to seem much more than they are if care is not taken to use models that closely resemble the human pathological condition and doses of drugs or microorganisms that attain similar blood and tissue concentrations in both animal and man.

In the 1920s, the theory of focal infection was widely taught as the cause of a wide range of illnesses with infected teeth as the principal source (5). All pulpless teeth were a probable focus of infection and the extraction of healthy teeth was justified to prevent focal infection (5). Endodontic education was eliminated in most United States dental schools (5). C Edmund Kells (39), the founder of dental radiology, was one of the few dissenting voices describing the indiscriminate extraction of teeth as 'the crime of the age' and recommending that dentists refuse to operate on physicians' instructions to needlessly remove teeth.

With the advent of the 1930s, some began to observe that: 'If this craze of violent removal goes on, it will come to pass that we will have a gutless, glandless, toothless – and I am not so sure that we may have, thanks to false psychology and surgery, a witless race' (40) and as stated in the American Journal of Ophthalmology: 'Stripped of tonsils and teeth, often the victim of colonic irrigation, abdominal, and genitourinary operations, the patient may finally be reduced to only those organs necessary for existence, while all the time his ocular disease progresses remorsely to blindness' (41). Such surgery for focal infection was three times more common in the rich than the poor in England and Wales and twice as common among the rich in the United States (42).

In 1935, Cecil and Angevine (43) published an analysis of 200 cases of rheumatoid arthritis that documented no benefit from tonsillectomy or dental extractions, but rather occasional exacerbations of the arthritis and concluded that: 'focal infection is a splendid example of a plausible medical theory which is in danger of being converted by its enthusiastic supporters into the status of an accepted fact,' and that 'the time has arrived for a complete reevaluation of the focal infection theory.' In 1939, Vaizey and Clark-Kennedy (44) demonstrated that patients made edentulous for 'medical reasons' developed subsequent arthritis and dyspepsia and that edentulism actually caused indigestion rather than cured it.

In 1940, Reimann and Havens (42) published the most influential critique of focal infection theory and observed that: (1) the theory of focal infection had not been proved, (2) its infectious agents were unknown, (3) large groups of people whose tonsils are present are no worse than those whose tonsils have been removed, (4) patients whose teeth and tonsils are removed often continue to suffer from the original disease for which they were removed, (5) any beneficial effects can seldom be ascribed to surgical procedures alone, (6) beneficial effects that occasionally occur after surgical measures are often outweighed by harmful effects or no effects at all and (7) many suggested foci of infection heal after recovery from systemic disease or when general health is improved with hygiene and dietary measures. It is of interest to note that only bodily areas superficially accessible to surgery were listed as foci of infection while deeper structures were conspicuously absent leaving one of its harshest critics to comment that a focus of infection was: 'anything readily accessible to surgery' (43).

As with many theories that attempt to 'explain it all' and thus appeal to the human psyche, the focal infection theory was elegant in its simplicity and offered quick and easy, albeit expensive (or from another prospective lucrative), solutions to a multitude of diseases for which medicine had (and still may have) no answer. It was easy

to deflect accusations of ignorance by directing blame to less defensible victims: dentists and patients. Little attention then as now was paid to the observations that temporal associations are the weakest of epidemiological links and that many of its proponents were infected with the concept of 'after it, therefore because of it' for which even today there is no preventive vaccine.

The new age

VGS have been isolated from infections in virtually every body organ and many disease processes: pneumonia, pleural empyema, mediastinitis, pericarditis, endocarditis, septic thrombophlebitis, conjunctivitis, otitis media, meningitis, osteomyelitis, cellulitis, sinusitis, brain abscess, prosthetic joint infections, cholangeitis and liver, lung and splenic abscesses (45, 46). These infections are similar to those that would occur in the oral cavity with the same microorganisms. VGS are classic purulence-producing microorganisms. Such infections are not unexpected as VGS are ubiquitous in the body (skin, conjunctiva, oral cavity, pharynx, gastrointestinal and genitourinary tracts), possess adhesins that allow attachment to virtually any body surface and are classically opportunistic bacteria that initiate infections only when host tissues are damaged, altered or diseased. The question is not whether these bacteria produce metastatic disease, but rather how often and what can be done, if anything, to prevent them.

In a study of *Streptococcus milleri* (*S. anginosus*, *S. intermedius*, *S. constellatus*) bacteremia, these organisms were present in 1.6% of all bacteremias (46). In 51 cases of *Streptococcus milleri* infection, 23 were liver abscesses, 14 pneumonia, six cervicofacial, five in the lung and four in the brain, with 78.4% occurring in patients with underlying disease states (45). In an analysis of 281 747 consecutive blood cultures over an 8-year period at the Mayo Clinic of which 20 456 were microorganism-positive, 2.8% were VGS and 4.4% were obligate anaerobes, some of which are found in the oral cavity: *Fusobacteriun nucleatum*, *Prevotella intermedia* and *Veillonella* (47). The prevalence of oral obligate anaerobes was very low: *Prevotella* (0.1%), *Fusobacterium nucleatum* (0.2%), *Peptostreptococcus* (0.2%), *Veillonella* (0.1%) and *Abiotrophia* (0.4%) (47). From these data, it is reasonable to conclude that oral microorganisms constitute only a very limited presence in bacteremic cultures.

Only four cases of septic arthritis ascribed to VGS are reported in the literature (48). It has been estimated that 2.0% of streptococcal meningitis is caused by VGS (49). In a retrospective analysis of the risk from oral bacteremias in 77 patients receiving stem cell and bone marrow transplants, no correlation was detected between radiographic periodontal status and mortality from septicemia with not a single periodontal pathogen isolated from septicemia in these patients (50). In a case report and review (51), a carotid artery mycotic aneurysm was allegedly caused by a dental extraction-induced *Pseudomonas aeruginosa* isolate with five other such cases from microorganisms also attributed to dental treatment (the mold *Penicillium*, *Klebsiella pneumoniae*, *Bacteroides fragilis*, *Salmonella typhi* and *Staphylococcus aureus*) that are rarely, if ever, associated with dental treatment-induced bacteremia and are also found in much higher concentrations elsewhere in the body. It remains a mystery as to why these reports still occur today with such certainty that these bacteremias originate from the mouth when no genetic microorganism identification is ever performed to give credence to such conclusions.

It is apparent from well-performed studies on the incidence and prevalence of metastatic infections with oral microorganisms that such bacteria are rarely a cause of systemic disease. Obligate oral anaerobes do not appear to survive well in other body locations and VGS are not primary pathogens but rather opportunistic bacteria that usually require altered biologic tissue to produce their suppurative effects. As aptly stated by Thomas Henry Huxley: 'The great tragedy of science: the slaying of a beautiful hypothesis by an ugly fact.'

Documented focal infections

The three most documented, publicized and litigated examples of focal infection are bacterial endocarditis, brain abscess and orthopedic prosthetic joint infections. Opinions abound on many aspects of these infections, but little attention has been paid to the absolute risk to the patient that these infections pose from dental-treatment-induced bacteremias (Table 1)

Bacterial endocarditis

The most visible and investigated focal infection is the metastasis of microorganisms from various body locales

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Table 1. The absolute risk rate (ARR) for various metastatic focal infections from a single dental treatment procedure (see text for data and assumptions).

Brain abscess: 1 per million to 1 per 10 million dental procedures
Prosthetic joint infection: 1 per 2.5 million dental procedures
Bacterial endocarditis
(1) If all general population VGS cases caused by dental treatment: 1 per 142 578 procedures
(2) If only 1% of VGS cases cause by dental treatment: 1 per 14 258 714 procedures
(3) Previous endocarditis: 1 per 95 058 dental procedures
(4) Cardiac valve prostheses: 1 per 114 069 dental procedures
(5) Rheumatic heart disease: 1 per 142 258 dental procedures
(6) Congenital heart disease: 1 per 475 290 dental procedures
(7) Mitral valve prolapse with regurgitation: 1 per 1 096824 dental procedures

(most notably the skin, mucosa, oral cavity and GI and GU tracts) to a damaged valve of the heart to infect a non-bacterial thrombotic endocarditis or vegetation (NBTE or NBTV). Due to injury to the cardiac valves (mostly the mitral and aortic valves), a layer of platelets and fibrin (the NBTV or NBTE) deposit on these valves and incorporate circulating bacteria or fungi into this matrix resulting in bacterial or infective endocarditis.

In the United States, the annual incidence of infective endocarditis (not all endocarditis is caused by bacteria) is about 11 200 cases (1500 in Great Britain), with approximately 25% caused by VGS and the majority now by staphylococci (52). Periodontal pathogens are a very rare cause of endocarditis with less than 150 cases reported in the literature (52). VGS as the etiologic agent of bacterial endocarditis has declined from 40% to 25% in recent years possibly because nosocomial (hospital-acquired) staphylococcal endocarditis has reached 25% of the total number of endocarditis cases.

Dental professionals have been routinely blamed for all endocarditis due to VGS, even though these microorganisms are ubiquitous in the body. It has been alleged without any documentation that 8–30% of all endocarditis is caused by dental treatment or dental disease (52), while new case-control studies indicate that there may be no association between dental treatment procedures and bacterial endocarditis (53, 54).

It has long been appreciated that random bacteremias resulting from daily oral hygiene procedures and mastication can produce an incidence of bacteremia approaching that of dental treatment procedures: tooth brushing (0–26%), dental flossing (20–58%), wooden cleansing devices (20–40%), water irrigation devices (7–50%) and mastication (17–51%) vs. tooth extraction (40–89%), periodontal surgery (36–88%), scaling and root planing (8–80%), simple prophylaxis (0–40%), buccal local anesthetic injection (16%), intraligamentary injection (97%), rubber dam and/or wedge/matrix band placement (9–32%) and endodontic treatment (0–15%) (52). Since the lymphatics, and not blood vessels (where the pressure gradient is outward and not inward after trauma), may be the primary means of entry of oral bacteria into the blood, mastication, and not trauma, may be the most important cause of oral bacteremias (52). There are no data on precisely how many microbes are necessary (inoculum size) to initiate any focal infection and little on the magnitude of the bacteremia (number of cfus in the blood) seen with orally induced bacteremias. Considerable controversy exists regarding the relation of oral gingival inflammation and degree of operation trauma to the incidence and magnitude of bacteremias ranging from none to a significant effect (52).

Guntheroth (55) and Roberts (56) have well demonstrated that the risk of a bacteremias arising from normal daily living is 1000–8000 times more likely than from a dental treatment procedure. It then becomes impossible to determine causality in any case

of bacterial endocarditis purported to be caused by dental treatment, unless the microorganism in the infected cardiac valve is genetically identical to that in the oral cavity. Furthermore, because of the 1000–8000 times greater chance of any bacteremia originating from normal daily living functions it is equally impossible to determine if the bacteremia emanated from the dental treatment or a time before or after it. There is no way to clock bacteremias. It is time for the courts to recognize the scientific facts regarding bacteremias and focal infections and cease and desist from the prosecution and persecution of dental professionals for metastatic infections, particularly bacterial endocarditis.

Rarely has an absolute risk rate for bacterial endocarditis been determined. Epidemiologists are fond of using the relative risk rate rather than the absolute risk rate for a given event as the former makes the association appear much more significant. A relative risk rate doubling from 1 to 2 is a 100% increase in the event rate but if this doubling were to measure an absolute risk rate increase from 1 to 2/100 000 population then not only would the 'association' appear much less significant but also might be challenged on methodological grounds.

An absolute risk rate for endocarditis can then be calculated (Table 1) utilizing well-documented data and certain reasonable assumptions. If 250 million persons in the United States visit a dentist for treatment on an average of 1.6 times per year (400 million annual visits) and the annual incidence of infective endocarditis is 11 200 cases (280 million population with a risk rate of 4/100 000 person years) and with 25% caused by VGS (assuming that all 2800 cases due to VGS are caused by dental treatment), then the absolute risk rate *from a single dental procedure or visit* is 1/142 258 in the general population. If it is further assumed that only 1% of all VGS endocarditis is caused by dental treatment (28 cases annually), then the annual absolute risk rises to 1/14 258 714 in the general population with no known cardiac risk factors.

The studies of Strom et al. (53) and many others (38) have well documented that persons with certain cardiac disorders, particularly of the cardiac valves, are at much higher risk for endocarditis than the general population. The classic study by Steckelberg and Wilson (57) determined that while the incidence of infective endocarditis in the general population is 1.7–4.9 cases per 100 000 person-years, the risk rises to 300–740/100 000 person-years for previous endocarditis, 308–630/100 000 person-years for patients with cardiac valve prostheses, 380–440/100 000 person-years with rheumatic heart disease, a mean 120/100 000 person-years for congenital heart disease on down to 52/100 000 person-years for mitral valve prolapse with regurgitation. Utilizing these data the absolute risk for endocarditis from a single dental procedure rises substantially in previous endocarditis (1/95 058), cardiac valve prosthesis (1/114 069), rheumatic heart disease (1/142 258), congenital heart disease (1/475 290) and mitral valve prolapse with regurgitation (1/1 096 824) (52). Even with significant risk factors the absolute risk rate for endocarditis from a single dental treatment procedure is very low.

Brain abscess

Brain abscesses (focal suppuration in the brain parenchyma) have been alleged to have occurred due to metastatic bacteremias from the oral cavity primarily based on the observations that the predominant causative microorganisms are VGS and that most brain abscesses occur in the frontal and temporal lobes of the brain serviced by the middle cerebral artery (38). Microorganisms may reach the brain via three routes: (1) direct spread from an adjacent infected area (middle ear or sinuses), (2) direct head trauma or (3) hematogenous (metastatic) spread from a distant source (38).

Otitis media and sinusitis account for 50–60% of contiguous brain abscesses in the United States, but this percentage can vary significantly from country to country with lung infections being another important source (38, 58, 59). Approximately 20% of brain abscesses have no known source of infection (58, 59). For a brain abscess to occur it must be preceded by a usually asymptomatic nidus of necrotic brain tissue (infarct) to which it can localize (38).

The most common etiologic microorganisms for brain abscesses are the streptococci that are responsible for 52–80% of all isolated species (38) with the *Streptococcus milleri* group predominating (59). In a study of 1773 brain abscesses, 24% were caused by facultative streptococci, 12% anaerobic streptococci (*Peptostreptococcus*), 23% by staphylococci from head trauma, 11% by *Proteus mirabilis* from otitis media and 4% were caused by *Escherichia coli* (60), with rare isolates of *Haemophilus influenzae*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*,

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Streptococcus pneumoniae, *Fusobacterium nucleatum* and *Veillonella* (61). In the canine model of brain abscess (62) and human studies (63), the disease progression is: early cerebritis (days 1–3), late cerebritis (days 4–9), early capsule formation (days 10–14) and late capsule formation (day 14 or later) (38).

Brain abscesses are diagnosed at 1/10 000 hospital admissions in the United States (64, 65). The incubation period and time to hospitalization are critical determinants of potential causation. In a review of 235 cases and the relation between onset of symptoms and hospitalization, 33% presented to the hospital in less than 1 week, 50% in 1 week to 1 month, 14% in 1–3 months and 3–4% after 3 months (66). It has been estimated that 75% of patients with brain abscesses seek hospitalization within 2 weeks of the onset of signs and symptoms: fever, headache, focal neurological deficits, nuchal (neck) rigidity, seizures and papilledema (edema of the optic disk) (67). Between 73% and 83% seek hospitalization within one month (66, 68).

In 10 reasonably reliable cases of brain abscess alleged to have been caused by oral microorganisms, the mean incubation period (from onset of bacteremia to first signs and symptoms) was 18 days (range 4–60 days) (38).

In another study of well-documented cases, the incubation period was a mean 16 days (range 9–37 days) (67). These data suggest that the incubation period for brain abscesses from oral microorganisms is 16–18 days with a mean time to hospitalization of 12 days, while the mean time from onset of bacteremia to hospitalization is about 30 days (38).

The majority of clinical studies on brain abscess do not list the oral cavity as a potential focus of infection but in seven studies that do the incidence was 7% (38). In the worst-case scenario where 7% of all brain abscesses resulted from random oral bacteremias or dental treatment and with an incidence of brain abscess of 1.3 to 12/1 million population per year, the oral cavity may be responsible for 0.09–0.84 cases of brain abscess/million population/year (38). With bacteremia from daily living 1000–8000 times more likely than from dental treatment (51, 52), the absolute risk of a brain abscess being caused by dental treatment is minimally a one chance in a million to one in 10 million (38). To 'prevent' such a brain abscess with antibiotic prophylaxis (if such was ever proven to work) would require prophylaxis for all 1–10 million dental patients since the infarct that predisposes to brain abscess is usually unknown to the patient. If penicillin prophylaxis were employed, the benefit would have to be judged against the risk of anaphylactic death, which is at least 1/million courses of penicillin. This would result in a net loss of life with prophylaxis.

Prosthetic joint infections

It is now more than 20 years since the first reports appeared of a temporal association between dental treatment and prosthetic joint infections and since then there is still not a single literature report of a genetically identical oral microorganism released by dental treatment identical to the one causing the prosthetic joint infection. Meanwhile millions upon millions of antibiotics have been given to prevent this infection without cost- or risk-benefit determinations, knowledge of the natural history of the disease, its incubation period and the role of spontaneous oral bacteremias. In a study of bacterial contamination of implant sites for prosthetic joints *before* placement, 12.8% were contaminated with staphylococci, streptococci and gram-negative rods (69). While four cases of genetically identical *Streptococcus sanguis* have been isolated from mouths fully septic from caries, pulpal death and periodontal disease and infected prosthetic joints (none of which had any dental treatment) (70), there is yet to be a scientifically determined case of prosthetic joint infection due to dental treatment procedures.

More reasoned and scientific thought and effort resulted in a worst-case estimate of a possible 0.03–0.04% infection rate by oral microorganisms of prosthetic joints (30–40/100 000 prosthetic joints) (71, 72). If it is assumed that the risk of a bacteremia is 1000 times more likely from oral hygiene and mastication than dental treatment, then the absolute risk for a prosthetic joint infection from dental treatment (worst-case) is one in 2.5 million (38). The best-case scenario is that dental treatment does not cause prosthetic joint infections. As with brain abscesses the use of the penicillins certainly and possibly the cephalosporins as antibiotic prophylaxis to 'prevent' prosthetic joint infections may be associated with a net loss of life due to anaphylaxis (71, 73). This conclusion should be tempered with the possibility that up to 18% of prosthetic joint infections are associated with patient mortality. This high death rate, although very rare due to oral microorganisms, constitutes the only conceivable reason for antibiotic prophylaxis in dental patients with prosthetic joints in the face of the overwhelming

evidence that it is unnecessary or harmful and with no data that it is even effective.

There is no evidence to support the routine use of antibiotic prophylaxis to 'prevent' prosthetic joint infections (74, 75) and little to none to support the contention that patients with diabetes mellitus, rheumatoid arthritis, immunosuppressive diseases, hemophilia, systemic lupus erythematosus and malnourishment are at greater risk for these infections than the general population. Many have interpreted the American Dental Association/American Academy of Orthopaedic Surgeons guideline of 1997 (74) as a mandate to employ antibiotic prophylaxis for such patients, which is incorrect. The guidelines clearly state that antibiotic prophylaxis is never mandatory for any of the patients and only 'should be considered' for these allegedly medically compromised patients. Data from the Mayo Clinic indicate that the rate of prosthetic joint infections from hematogenous sources declines very rapidly with time and reaches a low level plateau incidence 2 years after placement (76).

Endodontics and focal infection

Numerous studies have attempted to determine the significance of various microbial pathogens in pulpal and periapical infections (77). Efforts have been hampered by small sample sizes, lack of randomization or use of consecutive cases, varied case definitions and lack of documentation regarding the presence/absence of dental caries and periodontal disease, different expertise in culturing techniques, varied health status of patients and potential microbial contamination during sampling procedures.

In spite of these difficulties, sufficient data exist to establish that all orofacial infections of whatever origin share common major microbial pathogens: VGS, *Porphyromonas gingivalis*, *Prevotella intermedia, Veillonella*, *Fusobacterium nucleatum*, *Peptostreptococcus micros*, *Bacteroides forsythus*, *Eubacteria*, *Lactobacilli* and *Actinomyces* (77). Other less common or rare pathogens include *Propionibacterium acnes*, *Candida albicans*, *Enterococcus*, staphylococci, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Eikenella corrodens*, *Corynebacterium*, *Selenomonas* and *Wolinella recta* (77). Precisely how many of these rare microorganisms are contaminants is unknown. Oral pathogens with possibly greater relevance to pulpal pathology include *Dialister pneumosintes* and *Eubacterium* (78, 79) and *Prevotella endodontalis* (80). The relative importance of these pathogens in pulpal, periapical and periodontal infections, or pericoronitis, periimplantitis and infectious spread to contiguous areas (orbital, submandibular, mediastinal) are primarily quantitative rather than qualitative (77). Any orofacial infection spreading rapidly is likely to have a substantial VGS component (77).

The precise risk of bacteremia associated with endodontic lesions and therapy is subject to some controversy. Apparently no study exists that delineates the incidence/magnitude of spontaneous bacteremias from infected root canals with chronic periradicular lesions (81) nor any with acute periodontal abscesses. Such bacteremias may occur during the management of infected root canals and a good understanding of their incidence/magnitude would be of importance.

Bender et al. (82) determined a 0–15% incidence of bacteremia with none if the instrumentation remained within the canal and 15% if it extended beyond the apex.Baumgartner et al. (83) found a 3.3% incidence with non-surgical endodontics and a 83–100% incidence with surgical endodontics. In a study that intentionally instrumented beyond the apex, a 34–54% incidence of bacteremia was detected (84). Al-Karaawi et al. (85) determined that the 'cumulative' bacteremias with a rubber dam clamp in children was 175 times greater than a tooth extraction, while a matrix band was only four times greater which conflicted with another study by the same group that the incidence of bacteremia using a rubber dam/wedge/matrix band model was 9–32% (86). One of the difficulties with comparing any given dental procedure using cumulative data to dental extractions is that no determination has ever been made of how long dental extraction sites produce bacteremias during their healing phase.

Whether instrumentation has occurred beyond the apex may not be readily determined (87) and antibiotic prophylaxis for endocarditis prevention would be appropriate if the best clinical judgment of the dentist is that such a determination cannot be made. The question of bacteremias arising from rubber dam application should be clarified as the degree of trauma associated with its use is a likely variable. It is reasonable to conclude from the above data that non-surgical endodontics is may be the least likely of dental treatment procedures to produce significant bacteremias in either incidence or magnitude.

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It is claimed that endodontically treated teeth are always 'infected' (88) as it may be impossible to fill all lateral and accessory canals or eliminate the 'slime' layers on root canal surfaces. Whether this criticism is accurate or not may be irrelevant as it does not recognize basic microbiological principles of the inoculum effect (the threshold level of bacteria necessary to produce an infection), that the presence of bacteria does not *per se* define an active infectious process and that most microorganisms associated with the human body are either innocuous or beneficial. VGS in the oral cavity are antagonistic to periodontal pathogens and are a marker of good periodontal health (89, 90). The skin is protected from infection by streptococci, staphylococci and antimicrobial peptides. Many microbes in the gastrointestinal tract are beneficial to the host by aiding in digestion and providing colonization resistance against foreign pathogens.

It is appropriate to require those who promote endodontically treated teeth as a focus of infection to do so in a manner that is scientifically appropriate: with controlled clinical studies that determine the incidence/prevalence of diseases attributed to pulpal and periapical bacteremias following the rules of epidemiological evidence (91, 92), interventional studies to determine what measures can be employed to reduce such harm if it exists and risk- and cost-benefit determinations of any proposed remedies. Studies must also be performed to determine if endodontic treatment is inferior to alternate treatments such as implants, prosthetic replacements or no treatment other than extraction. To date, these studies have not been performed and there is no evidence to support the theory that modern endodontic therapy is not safe and effective.

Antigenic (molecular) mimicry

A number of rare disorders have been postulated to result from autoimmune mechanisms elicited by antigenic mimicry whereby endogenous or exogenous entities (bacteria, viruses, environmental contaminants) that resemble (mimic) a segment of an anatomical location and thereby antibody formation which, through largely inflammatory processes, damage the targeted tissue. To date, no oral microorganisms have been implicated but with the history of focal infection being prepared is always in order.

Of greatest interest currently is the relation of PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections), Sydenham's chorea (following rheumatic fever) and Tourette's Syndrome with recent Group A beta-hemolytic streptococcal (GABHS) infections, usually streptococcal sore throat (93, 94). These disorders share a common symptomatology (vocal and muscular tics, obsessive–compulsive disorder and attention deficit hyperactivity disorder), B lymphocyte D8/17 antigen (a marker for chorea associated with rheumatic fever) and antigens (antistreptolysin O, anti-Dnase B) to the M protein from streptococcal cell walls. Currently, it appears that children developing these disorders are a predisposed subtype since GABHS infections are very common, but PANDAS and Tourette's Syndrome are very rare. Additionally, many 'normals' have the same antistreptococcal antibodies and it is still unknown whether the antibodies are the result or cause of the diseases (93, 94).

Guillain–Barré syndrome (an acute inflammatory demyelinating polyneuropathy) has been suspected to be associated with *Campylobacter jejuni*, Epstein–Barr virus or *Mycoplasma pneumoniae* infections (95). Sarcoidosis has been postulated to be associated with human herpes virus 8 (HHV-8) (96) and amyotrophic lateral sclerosis to HTLV-1 and HIV microorganisms (97, 98). Multiple sclerosis has long been thought to be associated with the measles virus, Epstein–Barr virus, HHV-6 and various retroviruses, but it is more likely that multiple sclerosis is a multifactorial disease (99, 100). Presently, only myasthenia gravis fulfills all the criteria for an autoimmune disease (101).

Oral microorganisms and cardiovascular disease

Current interest in the potential association between oral microorganisms and cardiovascular disease is intriguing and has recently undergone scrutiny (10). Based upon the 'response to injury' theory of atheroma formation, it is hypothesized that the initial 'fatty streak' seen in the very early stages of atherosclerosis can be initiated by microorganisms that deposit in the region, promote the release of proinflammatory cytokines from damaged tissue and macrophages resulting in the formation of complex atheromas and/or the destabilization of the atheroma and subsequent thrombogenesis

and arterial occlusion (10). This hypothesis is elegantly simple and a classic example of focal infection. Unfortunately it is also simplistic.

Voluminous reports pervade the literature on various microorganisms or commonly their non-viable DNA as the etiologic agents for initial or subsequent injury to vascular endothelium: *Chlamydia pneumoniae*, *Helicobacter pylori*, cytomegalovirus, other herpes viruses, streptococci, staphylococci and periodontal pathogens (10). All these reports suffer from a serious flaw: none report other microorganisms that are present, but only the one the investigator is investigating. None acknowledge that if others are finding different microbes, then it is just possible that many are present and not only the one in a given study. This is a good example of a 'targeted study' and the 'disregard syndrome' that does not acknowledge conflicting data. It is apparent from the multiplicity of the microorganisms in atheromas (a sticky, convoluted substance) that this inflammatory response may result from any and all microbial entities that pass virtually endlessly during an individual lifetime.

Cardiovascular disease is a classic multifactorial disease with over 100 risk factors and markers along with gene polymorphisms that control the progress of the atheroma and initiate thrombogenesis (10). Dental studies to date have rarely if ever controlled for even the most acknowledged and important of these risk factors: the coronary lipid profile, hypertension, diabetes mellitus, obesity, sex, age, socioeconomic factors, lifestyle stress, homocysteine levels and most importantly, smoking and genetics (10). Granted this may be difficult and expensive but without these controls we have nothing more than another hypothesis. More recent and thorough studies indicate a very limited, if any, association between periodontal disease and cardiovascular disease (102–105) particularly if the studies are well controlled for smoking (106).

Epidemiological data can only determine possible causation by the use of interventional studies that decide whether the elimination of a variable alters the onset or course of the disease (91, 92). Even then, valid questions arise with oral diseases (gingivitis and periodontitis) with a potential lifetime of activity: will a single intervention (i.e. periodontal therapy including surgery) alter the course of the disease, will a series of interventions (periodontal maintenance) succeed, will none of these alter the disease and how many studies will be necessary by independent scientists to establish validity and finally what will be the ultimate risk and cost-benefit determinations. Dentists who are presently advising patients that various forms of dental treatment will reduce their risk for myocardial infarction and stroke (atherosclerotic disease) should refrain from this practice until there is substantial credible scientific evidence that such is the case. This unfortunate advice to patients is no more scientific today than the '100 percenters', 'therapeutic edentulism' and 'the clean sweep' were in the heydays of The Theory of Focal Infection.

Conclusions

Once again it appears that the Focal Infection Theory fails to pass scientific scrutiny. While isolated reports of focal infections appear, there is no evidence that focal infections or even antigenic mimicry are responsible for anything other than sporadic abscesses/infections and possibly rare autoimmune disorders. Even infective endocarditis requires a very specific series of events beginning with susceptibility to infection (damaged cardiac valves), microorganisms (streptococci and staphylococci) possessing strong adherence properties, heightened microorganism virulence, platelet and fibrin deposition (non-bacterial thrombotic endocarditis), a suitable environment for the microorganisms to thrive and their ability to avoid the local host defenses in the heart if such are still intact. Possibly this model explains why focal infections are so very rare.

The Focal Infection Theory may appeal to those who desire or require a simple explanation for biologic events particularly of a catastrophic nature or when no explanation exists. Natural events are commonly complex, secretive, multifactorial and mystifying. Mother Nature is anything but simple and is never fooled.

Added in proof

The ADA/AAOS 1997 guidelines for antibiotic prophylaxis in dental patients with total joint replacements has been updated in 2003 (*J Amer Dent Assn* 2003: **134** (7): 895–899) and remains essentially the same with an added patient information form. As with the 1997 statement, the 2003 advisory does not mandate antibiotic prophylaxis for any artificial joint patient but allows for the dentist's clinical judgement regarding prophylaxis for certain patients possibly at

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greater risk for hematogenous bacteremias particularly within the first two years of placement.

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